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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/674,962
Filing Date: November 08, 2000
Appellant(s): HAUER ET AL.

Daniel Kim
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 11/24/04.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

This appeal involves claims 1-4.

Claim 6 is allowed.

Claim 5 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

Claims 7-18 are withdrawn from consideration as not directed to the non-elected invention, fusion proteins, nucleic acids and methods.

(4) Status of Amendments After Final

No amendment after final has been filed.

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1-4 stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5,846,821	Guerinot et al	12-1998
EP 406,814	Haymore et al	07-1990

Volz, J. "Molecular characterization of metal-binding polypeptide domains by electrospray ionization mass spectrometry and metal chelate affinity chromatography", Journal of Chromatography, vol. 800 (1998), pp. 29-37.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Volz et al (Journal of Chromatography) in view of Guerinot et al (5,846,821) and Haymore et al (EP 409,814).

Volz et al discloses at page 32, col. 2, a peptide fragment of ATPase (1-51) of formula HxHxxxCxxC. A species of this generic peptide fragment is disclosed at page 34, Fig. 2, compound (a), ATPase-439 (1-51). Volz further discloses at page 29, col. 1 that a number of peptides and proteins containing certain motifs of histidine and cysteine residues are known to specifically bind divalent transition metal ions. Typical binding sites for Cu+2, Zn+2 and Ni+2 ions comprise CxxC motifs. Volz also discloses that that the metal binding property of the peptide fragment reside in the presence of the two His and Cys residues. The specific peptide of Volz is encompassed by the generic claimed peptide of Seq. ID. 1 except the peptide fragment of Volz has Leu at position 9(which corresponds to the claimed position X3 of Seq. ID. No. 1) instead of Ile as claimed. (This is based on X3 being Ile and the other X variables being any of the 20 naturally occurring amino acid residues, as recited.) However, Guerinot discloses at col. 14,

line 27 that conservative amino acid residues e.g., Leu and Ile can be substituted with one another, especially in the non-essential positions. Ile is a known homolog of Leu. Haymore, like Guerinot, discloses at page 4, line 12 peptide fragments that are metal binding peptides where the nature of the intervening residues is relatively unimportant. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to replace Leu in the peptide fragment of Volz with a homologous amino acid, Ile, as taught by Guerinot with a reasonable expectation of obtaining similar metal binding property. Guerinot teaches that Leu and Ile are conservative amino acid residues wherein one can replace the other without the loss of the peptide activity. Haymore, Guerinot and Volz all discloses that amino acids in the non-critical or intervening residues between the His and Cys metal binding residues are relatively unimportant in the binding of peptide fragments to metals. One would be motivated to substitute or find a homolog of Leu that are known to function equivalently in a peptide, in a structure-activity study of peptide, to ascertain whether the homologous peptide has an improved property.

(11) Response to Argument

Appellants argue that Volz et al do not teach anything about a method using the motif HxHxxxCxxC for the purification of other proteins or fusion proteins between said motif and other proteins. Appellants further argue that appellants' own studies have shown that these ATPase binding sites display a binding affinity which is too low for efficient purification of all desired proteins (specification page 2, lines 40-45). Appellants' sequences bind to immobilized metal ions at least 1.5 times more strongly than the Helicobacter pylori ATPase-439 (page 9, lines 28-32 and page 14, lines 39-46) and are therefore useful for the purification of a lot of proteins. By using the advantageous sequences, it is possible to purify proteins in a very high yield (page 14, lines 43 to 46). Nothing is mentioned about this in Volz et al therefore, appellants do not see why the skilled worker should consider Volz et al.

In response, appellants' arguments are not commensurate in scope with the claims and are unclear (In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993); MPEP 2144). The claims do not recite for a method by which Seq. ID. 1 is used to purify other proteins or fusion proteins. Rather, it recites a compound. Neither does the specification disclose the use of said Seq. ID. No. 1 to purify other proteins or fusion proteins,

as alleged. A review of page 14, lines 43-46 does not recite that the sequences have been advantageously used to purify other proteins. Said section states that "…. advantageous sequences make it possible for the protein yield after purification to be at least 20%…" In the subsequent page 15, lines 1-5 the specification states "..the process according to the invention for screening the nucleic acid library is advantageously suitable for automation. This process can be used easily for testing a large number of nucleic acid fragments and protein fragments for their metal ion binding affinity in so-called high-throughput screening…" There is nothing in these sections that indicate Seq. ID. 1 has been used to purify other proteins or fusion proteins. The instant specification, like Volz, discloses that proteins or peptide fragments containing a HxHxxxCxxC motif can be purified by its binding to metal ions. Appellants' sequences with a binding affinity of only 1.5 times stronger than the sequences of Volz could hardly be considered an advantage (and would appear more an experimental error value.) Furthermore, it is not apparent from the numerous possible combinations of amino acids in Seq. ID. 1, if all of the peptide sequences exhibit the alleged 1.5 stronger effects. [It is of interest to note page 21, lines 10-13 of the instant specification. It describes that only clone M13 shows the

alleged advantageous result while the other clones M14-16 showed no binding to Ni metal chelate columns, page 19, lines 40-41.] In showing "unexpected" results appellants must establish that there actually is a difference between the results obtained through the claimed invention and those of the prior art, that the difference actually obtained would not have been expected by one skilled in the art at the time of the invention, and that the difference is of practical advantage. Compare In re Freeman, 474 F.2d 1318, 177 USPQ 139 (CCPA 1973), In re Klosak, 455 F.2d 1077, 173 USPQ 14 (CCPA 1972) and In re D'Ancicco, 452 F.2d 1060, 172 USPQ 241 (CCPA 1972). Furthermore, Volz discloses or at least suggests, at page 35, Fig. 4, that multiple affinities to the metal column by a single protein (ATPase) may be explained by different metal ion-binding sites within the same sequence. The region between the phosphorylation site and the ATP-binding site contains a considerable number of His and Cys residues that may constitute further metal ion-binding sites.

Appellants argue that the sequence fragment disclosed by Guerinot, His-Gly-His-Gly-His-Gly-His-Gly, is totally different from the claimed protein fragments. Also, that at col. 14, line 27 Guerinot discloses a general teaching that the amino acids Ile and Leu belong to the group of amino acids which have

uncharged side chains and therefore a skilled worker would change the codon usage of a given nucleic acid sequence coding for example for Leu to the codon usage of Ile in the event he is interested in mutagenizing the said sequence without changing the activity of the enzyme encoded by the sequence. These types of changes are only possible as disclosed by Guerinot et al in areas, which are not essential for the activity of the MRP proteins (see col. 14, lines 30 to 33).

In reply, as recognized by appellants, Guerinot discloses that the substitution of Leu for Ile is only possible in areas, which are not essential for the activity of a protein. It is for this disclosure that that Guerinot is employed, not for the sequences, as argued. It would be within the ordinary skill in the art to make this substitution in the sequence of Volz since Volz discloses that this residue is not essential for binding activity. Volz positively teaches the essential or critical residues for metal ion binding are the His and Cys residues. The intervening residues can be any of the residues found in the natural protein (i.e., naturally occurring residues). There is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosure taken, as a whole would suggest to one of ordinary skill in the art. In re Simon 174 USPQ 114

(CCPA 1972); In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969).

Appellants argue that Haymore et al teach different proteins for immobilized-metal affinity chromatography. The sequences disclosed by Haymore et al are composed of two histidine residues, one histidine residue and one aspartic acid residue. Nothing is mentioned about two histidine and two cysteine residues in combination.

In response, Haymore is employed not for the sequences as argued as Volz discloses the claimed sequence. Rather, for its disclosure as to the essential or non-essential residues that are metal ion binding. As stated by applicants, Haymore discloses one histidine and one aspartic residue. Variant proteins and polypeptides with said histidine or aspartic residue at one or more position are taught by Haymore to have an enhanced affinity i.e., greater binding strength for immobilized-metal affinity resins.

Appellants believe that the examiner would only have arrived at the claimed invention by picking and choosing the elements and the knowledge was not within the level of ordinary skill at the time the claimed invention was made.

In reply, the positive teaching of Volz of a compound species encompassed in the prior art (and claim) generic formula HxHxxxCxxC can be hardly considered picking and choosing of elements. Rather, an express teaching of the claimed elements. Nevertheless, to pick and chose (select) features from the prior art to effect results expected from these features is within the purview of 35 USC 103. In re Skoner, 186 USPQ 80 (CCPA 1975);In re Schaumann, 572 F.2d 312, 316, 197 USPQ 5,9 (CCPA 1978) [This is evident from appellants' Seq. ID. 1. Appellants pick and choose at least ten residues from the 20 naturally occurring residues(present in the prior art natural proteins). The at least ten residues are then assigned for one of the X variables (e.g., X1) with the rest of the X variables (X2-X6) being any one of the 20 naturally occurring residues].

The combined teachings of the prior art therefore render the claimed compounds prima facie obvious.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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Primary Examiner
Art Unit 1639

tdw
February 18, 2005

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